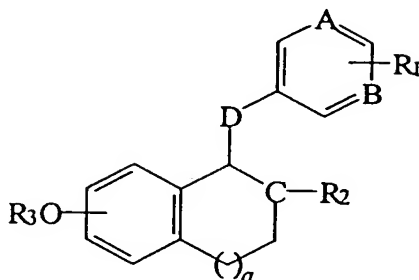


## CLAIMS

1. A compound having the structure:



and stereoisomers and pharmaceutically acceptable salts thereof;

wherein

$a$  is 0, 1 or 2;

A, B and C are independently CH, CR or N;

D is  $-(CH_2)_r-$  or  $-(CH_2)_nC(=O)(CH_2)_m-$ ;

$R_1$  represents one or two substituents independently selected from -X-Y;

$R_2$  is  $C_{1-8}$ alkyl,  $C_{6-12}$ aryl,  $C_{7-12}$ aralkyl,  $-C(=O)R_5$ , a five- or six-membered heterocycle or heterocyclealkyl containing up to two heteroatoms selected from O,  $NR_c$  and  $S(O)_q$ , or a bicyclic ring system contain a five- or six-membered heterocycle fused to phenyl, wherein each of the above groups are optionally substituted with one to three substituents independently selected from -X-Y or  $R_4$ ; and

$R_3$  is hydrogen,  $-R_6$ ,  $-(CH_2)_5C(=O)R_6$ ,  $-(CH_2)_5C(=O)OR_6$ ,  $-(CH_2)_5C(=O)NR_6R_7$ ,  $-(CH_2)_5C(=O)NR_6(CH_2)_nC(=O)R_7R_8$ ,  $-(CH_2)_5NR_6C(=O)R_7$ ,  $-(CH_2)_5NR_6C(=O)NR_7R_8$ ,  $-(CH_2)_5NR_6R_7$ ,  $-(CH_2)_5OR_6$ ,  $-(CH_2)_5SO_qR_6$  or  $-(CH_2)_5SO_2NR_6R_7$ ;

and wherein

$R_4$  is at each occurrence independently halogen, hydroxy, carboxy,  $C_{1-6}$ alkyl,  $C_{1-4}$ alkoxy,  $C_{1-4}$ haloalkyl,  $C_{1-4}$ acyloxy,  $C_{1-4}$ thio,  $C_{1-4}$ alkylsulfinyl,  $C_{1-4}$ alkylsulfonyl, (hydroxy) $C_{1-4}$ alkyl,  $C_{6-12}$ aryl,  $C_{7-12}$ aralkyl,  $-C(=O)OH$ ,  $-C(=O)OR$ ,  $-OC(=O)R$ ,  $-C(=O)NHR$ ,  $-C(=O)NRR$ ,  $-C(=O)NHOR$ ,  $-SO_2NHR$ ,  $-NHSO_2R$ ,  $-CN$ ,  $-NO_2$ ,  $-NH_2$ ,  $C_{1-4}$ alkylamino,

C<sub>1-4</sub>dialkylamino, -NHC(=O)R, NHC(=O)(CH<sub>2</sub>)<sub>5</sub>(five- or six-membered heterocycle), a five- or six-membered heterocycle, or a five- or six-membered heterocycle fused to phenyl;

R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> are at each occurrence independently hydrogen, C<sub>1-8</sub>alkyl, C<sub>6-12</sub>aryl, C<sub>7-12</sub>aralkyl, or a five- or six-membered heterocycle or heterocyclealkyl containing up to two heteroatoms selected from O, NR<sub>c</sub> and S(O)<sub>q</sub>, wherein each of the above groups are optionally substituted with one to three substituents independently selected from R<sub>4</sub>;

X is at each occurrence independently

a direct bond;

-(CH<sub>2</sub>)<sub>n</sub>Z(CH<sub>2</sub>)<sub>m</sub>-;

-O(CH<sub>2</sub>)<sub>n</sub>Z(CH<sub>2</sub>)<sub>m</sub>-;

-S(CH<sub>2</sub>)<sub>n</sub>Z(CH<sub>2</sub>)<sub>m</sub>-;

-NR<sub>c</sub>(CH<sub>2</sub>)<sub>n</sub>Z(CH<sub>2</sub>)<sub>m</sub>-;

-O(CH<sub>2</sub>)<sub>n</sub>CR<sub>a</sub>R<sub>b</sub>-;

-NR<sub>c</sub>(CH<sub>2</sub>)<sub>n</sub>CR<sub>a</sub>R<sub>b</sub>-;

-OCHR<sub>c</sub>CHR<sub>d</sub>-; or

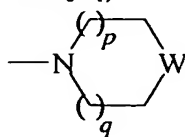
-SCHR<sub>c</sub>CHR<sub>d</sub>-;

Y is at each occurrence independently

halogen;

-R<sub>c</sub>;

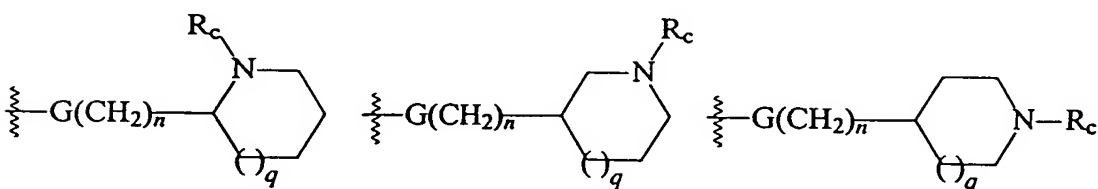
-NR<sub>c</sub>R<sub>f</sub>;

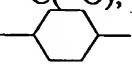


, optionally fused on adjacent carbon atoms with one or two phenyl or cycloalkyl rings, and with each carbon optionally and independently substituted with carbonyl or with one or two substituents independently selected from R<sub>4</sub>, with any two R<sub>4</sub> substituents on a single carbon atom optionally being taken together to form a five- or six-membered heterocycle, and with each nitrogen atom

optionally and independently substituted with  $R_4$ , wherein  $W$  is  $-NR_c-$ ,  $-O-$ ,  $-S-$  or  $-CR_cR_r-$ ; or a bridged or fused  $C_{5-12}$ bicyclic amine optionally substituted with one to three substituents independently selected from  $R_4$ ;

or where  $-X-Y$  is



$Z$  is  $CH_2$ ,  $CH=CH$ ,  $C\equiv C$ ,  $O$ ,  $NR_c$ ,  $S(O)_q$ ,  $C(=O)$ ,  $C(OH)R_c$ ,  $C(=O)NR_c$ ,  $NR_cC(=O)$ ,  $C(=O)NR_c$ ,  $NR_cC(=O)$  or ;

$G$  is  $O$ ,  $S$  or  $NR_c$ ;

$n$  and  $m$  are at each occurrence independently 0, 1, 2 or 3;

$p$  is at each occurrence independently 1, 2 or 3;

$q$  is at each occurrence independently 0, 1 or 2;

$r$  is at each occurrence independently 1, 2, 3, 4 or 5;

$s$  is at each occurrence independently 0, 1, 2, 3 or 4;

$R$  is at each occurrence independently  $C_{1-6}$ alkyl;

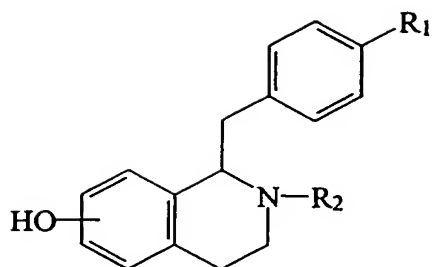
$R_a$  and  $R_b$  are at each occurrence independently  $C_{1-8}$ alkyl or taken together form a  $C_{3-8}$ cyclic alkyl;

$R_c$  and  $R_d$  are at each occurrence independently hydrogen or  $C_{1-4}$ alkyl; and

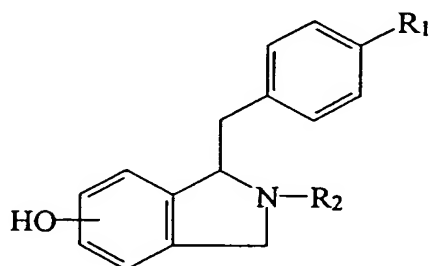
$R_e$  and  $R_f$  are at each occurrence independently hydrogen,  $C_{6-12}$ aryl,  $C_{1-8}$ alkyl,  $C_{7-12}$ aralkyl, a five- or six-membered heterocycle, or a five- or six-membered heterocycle-fused to phenyl; or wherein  $R_e$  or  $R_f$  form a 3-8 membered nitrogen-containing heterocyclic alkyl with  $R_a$  or  $R_b$ ; and wherein each  $R_e$  and  $R_f$  are optionally substituted with up to three substituents independently selected from  $R_4$ .

2. The compound of claim 1 wherein  $a$  is 1.

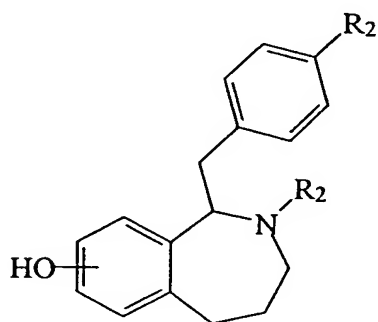
3. The compound of claim 1 wherein  $a$  is 0.
4. The compound of claim 1 wherein  $a$  is 2.
5. The compound of claim 1 wherein A and B are CH.
6. The compound of claim 1 wherein A is CH and B is CR.
7. The compound of claim 1 wherein A is CH and B is nitrogen
8. The compound of claim 1 wherein A and B are nitrogen.
9. The compound of claim 1 wherein C is nitrogen.
10. The compound of claim 1 wherein C is CH or CR.
11. The compound of claim 1 wherein D is  $-(CH_2)_r-$ .
12. The compound of claim 11 wherein  $r$  is 1.
13. The compound of claim 1 wherein D is  $-(CH_2)_nC(=O)(CH_2)_m-$ .
14. The compound of claim 13 wherein  $n$  and  $m$  are both 0.
15. The compound of claim 1 wherein A and B are CH, C is N and D is  $-CH_2-$ .
16. The compound of claim 15 wherein  $a$  is 1 and having the structure:



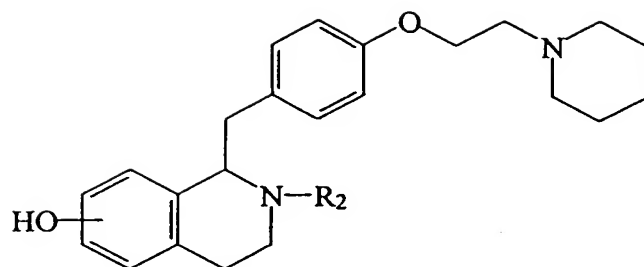
17. The compound of claim 15 wherein  $\alpha$  is 0 and having the structure:



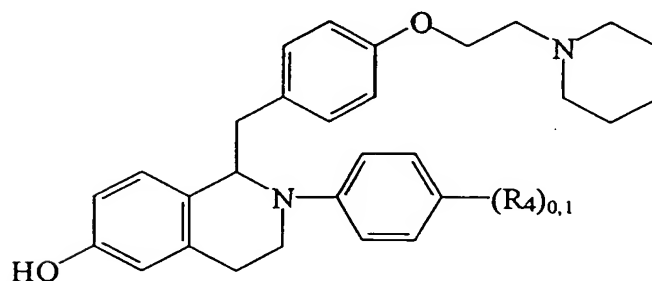
18. The compound of claim 15 wherein  $\alpha$  is 2 and having the structure:



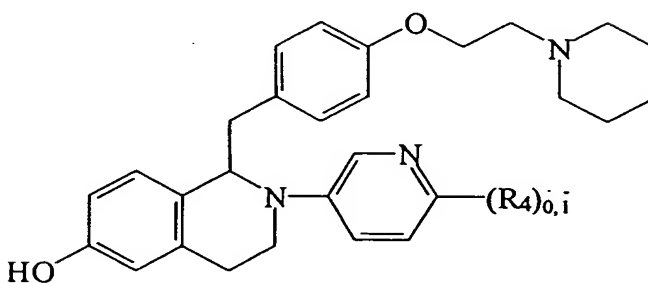
19. The compound of claim 16 having the structure:



20. The compound of claim 19 having the structure:



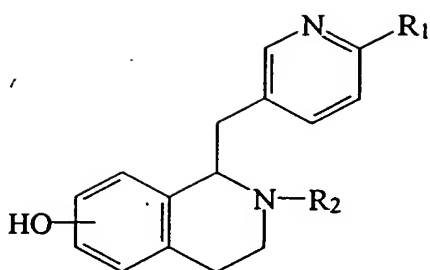
21. The compound of claim 19 having the structure:



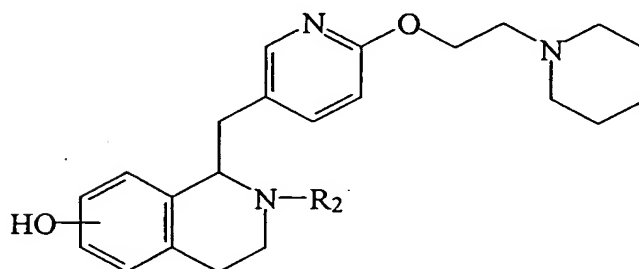
22. The compound of claim 19 wherein R<sub>2</sub> is C<sub>1-8</sub>alkyl.

23. The compound of claim 1 wherein A is nitrogen, B is CH, C is nitrogen and D is -CH<sub>2</sub>-.

24. The compound of claim 23 wherein *a* is 1 having the structure:



25. The compound of claim 24 having the structure:



26. The compound of claim 1 wherein A and B are N, C is N, and D is -CH<sub>2</sub>-.
27. The compound of claim 1 wherein A, B and C are CH, and D is -CH<sub>2</sub>-.
28. The compound of claim 1 wherein R<sub>1</sub> represents a single -X-Y substituent.
29. The compound of claim 28 wherein X is -(CH<sub>2</sub>)<sub>n</sub>Z(CH<sub>2</sub>)<sub>m</sub>-.
30. The compound of claim 29 wherein n is 0.
31. The compound of claim 30 wherein Z is oxygen.
32. The compound of claim 28 wherein X is a direct bond and Y is -R<sub>e</sub> or -NR<sub>e</sub>R<sub>f</sub>.

33. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier or diluent.

34. A method for modulating ER- $\beta$  in a cell expressing ER- $\beta$ , comprising contacting the cell with an effective amount of a compound of claim 1.

35. The method of claim 32 wherein the cell preferentially expresses ER- $\beta$  over ER- $\alpha$ .

36. The method of claim 35 wherein the cell is of bone, bladder, uterus, ovary, prostate, testis, epididymis, gastrointestinal tract, kidney, breast, eye, heart, vessel wall, immune system, lung, pituitary, hippocampus or hypothalamus cell.

37. A method for modulating ER- $\beta$  in tissue expressing ER- $\beta$ , comprising contacting the tissue with an effective amount of a compound of claim 1.

38. The method of claim 37 wherein the tissue preferentially expresses ER- $\beta$  over ER- $\alpha$ .

39. The method of claim 38 wherein the tissue is tissue of bone, bladder, uterus, ovary, prostate, testis, epididymis, gastrointestinal (GI) tract, kidney, breast, eye, heart, vessel wall, immune system, lung, pituitary, hippocampus or hypothalamus.

40. A method for treating an estrogen-related condition, comprising administering to an animal in need thereof an effective amount of a pharmaceutical composition of claim 33.

41. The method of claim 40 wherein the estrogen-related condition is breast cancer, osteoporosis, endometriosis, cardiovascular disease, hypercholesterolemia, prostatic hypertrophy, prostatic carcinomas, obesity, hot flashes, skin effects, mood swings,



memory loss, prostate cancer, menopausal syndromes, type-II diabetes, Alzheimer's disease, urinary incontinence, GI tract conditions, spermatogenesis, vascular protection after injury, endometriosis, learning and memory, CNS effects, plasma lipid levels, acne, hirsutism, solid cancers, multiple myeloma, lymphoma, hairloss, cataracts, natural hormonal imbalances, or adverse reproductive effects associated with exposure to environmental chemicals.

42. A method for inhibiting a cytokine in an animal in need thereof, comprising administering to the animal an effective amount of a compound of claim 1.

42. The method of claim 42 wherein the cytokine is IL-6

43. The method of claim 42 wherein the cytokine is GM-CSF.

44. A method for treating cancer associated with IL-6 in an animal in need thereof, comprising administering to the animal an effective amount of a compound of claim 1.